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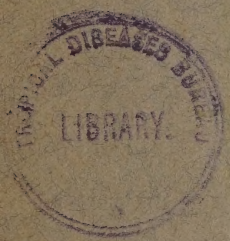
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DENGUE, ITS HISTORY, SYMPTOMATOLOGY AND
EPIDEMIOLOGY.

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DENGUE, ITS HISTORY, SYMPTOMATOLOGY AND EPIDEMIOLOGY.*

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It is a remarkable fact that a disease so striking in its [117]
tendency to appear in wide-spread epidemics and with so characteristic a symptomatology should not have been reported until about 1780 and then almost simultaneously by Gaberti in Egypt, Bylon in Batavia, Rush in Philadelphia and a year or two later by Cubillas in Spain.

While Hirsch (Handbook of Geographical and Historical Pathology) gives the credit for the first mention of the disease to the chronicler Gaberti, who describes a disease with certain resemblances to dengue as existing in Cairo in 1779, yet, for the reason that certain clinical features of this epidemic would hardly appear to belong to dengue, as we now know it, there would seem to be good ground upon which to give the credit of priority to our great American physician and statesman, Benjamin Rush, who, under the designation break-bone fever, gave us a true picture of dengue as it manifested itself in Philadelphia in 1780.

Gaberti was particularly impressed with the knee involvement so that from his description the disease was known as the [118]
disease of the knees. He further noted swelling of the fingers and that the pains continued for more than a month. The sudden onset and the sweating would seem to belong to relapsing fever as well as to dengue and in support of the view that the disease described by Gaberti might have been relapsing fever we have the statement of Sandwith (Medical Diseases of Egypt) that bone pain, chiefly of the knee, is the

* Paper read at a meeting of The Johns Hopkins Hospital Medical Society, February 3, 1913.

[118] symptom most complained of by the Egyptian native with relapsing fever.

Bylon, who reported an outbreak of an epidemic disease in Batavia in 1780, stated that everybody was attacked and that the symptoms were almost the same as those ushering in plague—headache, lassitude and pains in the joints. He noted, however, that this epidemic had no bad consequences, patients getting rid of it in three days under moderate diet and copious beverages.

Rush (Medical Inquiries and Observations, Philadelphia, 1789), in a chapter describing a bilious remitting fever, states that it first appeared in July and August, 1780.

Abstracting his description we note that hardly a family escaped and in many families scarcely a member. All ages were affected. The fever came on in different ways—in some a giddiness of the head marked the onset which attacked so suddenly as to produce even symptoms of apoplexy. It was a great surprise to Rush that persons so affected got well in two or three days. In some cases the onset came with delirium. The pain was exquisitely severe in the head, back and limbs. Pain in the forehead at times only occupied the eyeballs. In some cases the pains in the back and hips were so acute that the patient could not lie in bed. They all complained especially of soreness in the seats of their pains, particularly when in the eyeballs. The disease was thought by many to be a rheumatism, but its general name among all classes was break-bone fever. Nausea was common and in some instances vomiting occurred. There was a very disagreeable taste in the mouth. The exacerbations were more severe every other day. Relapses were frequent. A rash appeared on the third or fourth day which proved favorable. It was often accompanied by a burning of the palms of the hands and soles of the feet. Some who were not even confined to bed had these skin efflorescences. In some cases there were swellings under the jaw and about the ears. Discharges of blood from the nose frequently accompanied the fall of the fever on the third or fourth day while in others a profuse hæmorrhage from the nose or bowels about the eleventh day preceded a fatal issue. When the fever did not terminate on the third or fourth day it fre-

quently ran on to the fourteenth or even the twentieth day with [118] symptoms of typhus gravior. In some cases the fever was followed by jaundice. The fever declined in October when the weather became cool.

For treatment Rush recommended first a gentle vomit of tartar emetic which if given at the onset produced a crisis on the third or fourth day. If only nausea resulted he repeated the dose with the happiest effect. Salts and cream of tartar were given to open the bowels. After evacuating the stomach and bowels he gave small doses of tartar emetic mixed with Glauber salts. Rest in bed was recommended as it favored the eruption of the rash. Persons who struggled against the fever, trying to shake it off by labor or exercise, had a slow recovery. He gave bark about the third or fourth day and if the fever continued beyond the fourth day he used blisters to the neck and behind the ears.

As the fever was sometimes accompanied by symptoms of dysentery opium was very beneficial after the necessary evacuations had been made. As the pulse was never hard, but only full, Rush never had recourse to bleeding. Many other physicians practised bleeding and he notes in this connection "I am bound to declare that I heard of several cases in which bleeding was followed by a fatal termination of the disease."

Most of those who recovered complained of nausea and loss of appetite with a bitter taste in the mouth. Faintness, especially upon sitting up in bed, was often noticed. The most remarkable symptom during convalescence was an uncommon dejection of spirits.

When we analyze this description by Rush it must be immediately apparent to every one that cases of typhoid fever (hæmorrhage from the bowels about the eleventh day), malarial fever (the exacerbations were more severe every other day), probably yellow fever (in several cases the fever was followed by a jaundice) and dysentery (the fever was sometimes accompanied by symptoms of dysentery) were confused with dengue, yet it is remarkable that notwithstanding this fact we should be given such a clear picture of the most striking features of the disease under consideration.

As I have seen the disease it would appear to me to be best outlined as follows:

[118] I. A disease of strikingly sudden onset with rapidly rising temperature. Prodromata practically absent.

II. Very marked soreness deeply seated about the place of origin of the ocular muscles so that every movement of the eyeballs is at once complained of as giving pain.

III. General pains all over the body, more especially of the back and about tendinous insertions of the muscles which cause the pains to be referred to the joints. The rachialgia may be as great as that in variola or yellow fever.

IV. Fall of the fever about the third or fourth day which is often attended by a critical epistaxis, sweat or diarrhoea, to be succeeded by an intermission of from one to three days of a feeling of well being. About this time or with the secondary rise of fever the true dengue rash appears. This is at first noted about the bases of the thumbs and extending over the dorsal surfaces of the wrists. Almost simultaneously a measles-like rash appears over the dorsal and internal surfaces of the big toe extending to the ankle, especially over the internal malleolus. Later on the elbows and knees may be involved or the rash may cover thickly the entire body. A carmine flush of the palms of the hands and soles of the feet is not uncommon. The so-called primary eruption is nothing more than an initial flushing of the face.

[119] V. About the third day a marked slowing of the pulse is noted which may in the second accession of pyrexia be as low as forty-five beats per minute.

VI. There is a profound loss of appetite, interest and energy. These manifestations tend to extend well into convalescence. Insomnia or rather an inability to sleep for any extended period is often a marked feature of the disease. One dozes but does not sleep.

VII. There are no changes in the urinary findings which could be attributed to the disease.

VIII. Very characteristic is the blood picture, which may be well exhibited even by the second day. In one hundred cases in which I very carefully studied the blood the average leucocyte count was three thousand two hundred per cubic millimeter with a polymorphonuclear percentage of fifty-

one. My lowest white count in this series was one thousand [119] seven hundred and the lowest polymorphonuclear percentage twenty-nine. These results were obtained during a recent tour of duty in the Philippines. During a former tour I obtained lower results, but do not feel justified in attaching the same confidence to them as to those given above. These one hundred counts were made with a method in which the total count and the differential count were made in the same preparation. A one to twenty dilution of blood was made with $1\frac{1}{2}$ per cent of formalin in $\frac{1}{2}$ per cent glycerin in distilled water to which diluent had been added one drop of Giemsa's stock solution for every cubic centimeter. The formalin (40 per cent formaldehyd) should have a reading of plus one to phenolphthalein.

It had been my opinion formerly that the differential count other than that of the polymorphonuclears was of diagnostic value. I am now convinced that the type of leucocyte making up the percentage not taken up by the polymorphonuclears is inconstant, there being at times an increase in lymphocytes while again the increase may be in the large mononuclears and transitionals.

A few months ago my attention was called to the rather marked leucopenia and low differential count of the polymorphonuclears in the blood examination of a case of undetermined fever in a lady living in Washington. I telephoned her attending physician asking him if the patient had been recently out of Washington. He gave the information that she had come up from Florida only a few days previously. I then asked whether she complained of an intense soreness at the back of the eyeballs, next as to the presence of an unusually slow pulse and then as to an eruption. The answers to the first two questions were in the affirmative, but to the last negative. I then requested him to look for an eruption commencing about the dorso-lateral surfaces of the thumbs and great toes. Two days later the eruption appeared confirming my suspicions.

This case was thought by her physician to be one of influenza and it is in the blood count and slow pulse that we have our best points of differential diagnosis. Sandwith notes the

[119] value of the slow pulse in differentiating the two diseases in Egypt.

At the present time with a railroad trip of only two days separating us from Key West it will be appreciated how easy it would be for dengue cases to appear in the practice of the physicians of the North.

There have recently appeared many articles dealing with the question of the differentiation of dengue and various other dengue-like fevers such as phlebotomus fever, three-day fever, seven-day fever, sand-fly fever, etc., and, in many of these, great importance is attached to the characteristic of a slow pulse in them as compared with the more rapid pulse of dengue. This is an error, as I was more impressed by the constancy of the slow pulse in dengue than by any other symptom. In this connection it is remarkable that Rush makes no mention of a slow pulse in dengue because in his book on yellow fever (*An Account of the Bilious Remitting Yellow Fever, 1794*) the symptom which most attracted his attention was the slow pulse. In discussing at length the peculiarities of the pulse of yellow fever he states that he at first thought it due to some affection of the brain, but later ascribed it to a spasmodic affection accompanied with preternatural dilatation or contraction of the heart. Rush termed this pulse the indescribable or sulky pulse. He notes that it was present even in the very mild cases and he states that it was so familiar to him that he could have distinguished the disease without seeing the patient. It is remarkable that Touatre in his book on yellow fever should state that while physicians had observed the slowing of the pulse in yellow fever yet none understood its diagnostic value until Faget promulgated the law of the falling pulse.

Just here it may be noted that the most important consideration in connection with dengue is its differentiation from yellow fever. This differentiation rests best in:

(1) The normal urine of dengue and the albuminuria of yellow fever.

(2) The striking blood picture of leucopenia and marked diminution in polymorphonuclear percentage of dengue with normal findings in yellow fever.

(3) The jaundice appearing about the third day in yellow fever and the characteristic eruption in dengue showing itself from the third to the fifth day. [119]

Many of the English authorities in India have drawn attention to the susceptibility of kala azar patients to intercurrent affections, and this they attribute to the marked leucopenia of kala azar. Of course with the much shorter duration of the period of leucopenia in dengue there would be less liability to bacterial infection, but in my opinion this possibility should not be lost sight of.

A vigorous man, a corporal in the U. S. Marine Corps, had an attack of dengue while suffering from an impetiginous staphylococcic infection. The fever continuing the man was sent to Canacao hospital, where he was found to have a positive blood culture for *Staphylococcus pyogenes aureus*. Fifteen days from the onset of the dengue the man died and at the autopsy numerous miliary abscesses were found in kidneys, spleen and liver. It would seem reasonable to consider that the lowering of the phagocytic forces enabled the local staphylococcic infection to become generalized.

It is possible that this susceptibility to infection may explain the occasional appearance of enlarged glands in dengue, infections from tonsils causing glandular enlargement. As a matter of personal observation I can state that I have very rarely noticed any glandular enlargements in dengue and this notwithstanding careful search in order to verify this finding, which is rather prominently brought out by some authorities. [120]

Two of the most characteristic features of dengue were noted by Rush, viz.: the uncommon dejection of spirits and the slow recovery of those who struggled against the fever. It is a matter of common comment that the most frivolous person considers life a heavy burden during an attack of dengue—that the optimist becomes a rank pessimist. I can vouch for the statement that the only pleasure left to the dengue patient is the pleasure of solitude, there having been nothing I so desired while suffering from this disease as to be let alone. One of our naval officers suggested that an efficient method of ridding the service of practical jokers would be to furnish the dengue patients with large caliber revolvers and then persuade

[120] the jokers to have fun at the expense of the poor miserable dejected creatures.

The best proof of Rush's statement that struggling against the disease leads to a protracted convalescence is furnished by the experience of those on board the French ship *Cher* at the time of her being wrecked in New Caledonia, January 6, 1884. The accounts tell us that those who were in the first days of the disease did not want to be disturbed—they objected to being rescued. Others, however, who were recovering lent valuable assistance in the rescue work, but suffered, as a result, from a most protracted convalescence, some of them not having recovered their health two months later.

As regards the epidemiology of dengue there seems to be a general acceptance of the idea that dengue is transmitted by the common culicine mosquito of the tropics, *Culex fatigans*. There is not, however, that definiteness which attaches to the transmission of yellow fever by *Stegomyia calopus* or to pappataci fever by *Phlebotomus papatasi*, in both of which a certain period of development of the unknown filterable virus in the arthropod host is necessary before the insects become capable of transmitting the infections. It will be remembered that in the nine experiments as to dengue transmission, conducted by Ashburn and Craig, the authors threw out five of the cases for such reasons as previous immunity or refusal of the experimental mosquitoes to bite. Of the four remaining volunteers only one developed dengue. This man, however, had been on duty at the Division Hospital and the statement is made that he had not been exposed to the disease so far as could be determined. This of course rather militates against the value of this isolated experiment and furthermore the mosquitoes which bit him had fed on the blood of a dengue patient only two nights previously. If this is to be considered as a valid experiment, we must believe that only a short sojourn of the virus in the mosquito is requisite, which is rather at variance with the eleven days for the yellow fever virus and eight days for that of pappataci fever.

As regards the transmission of the disease by blood filtered through a diatomaceous filter it will be remembered that Ashburn and Craig, by proving this fact, placed the dengue virus

in the same category with the filterable viruses of the two [120] diseases just considered (Philippine Journal of Science, May, 1907). It should be stated that Doerr's report on pappataci fever was subsequent to that of Ashburn and Craig (Berlin Klin. Woch., 1908, No. 41).

Graham in Beirut carried out some experiments, one of which would seem to almost positively demonstrate mosquito transmission. He took mosquitoes which had fed on dengue patients, to a village in the mountains where no case of dengue existed. He caused these mosquitoes to feed on two natives of the village and both men became sick with dengue four and five days respectively after being bitten by the mosquitoes. Graham's claims to have noted piroplasma-like organisms in dengue blood have not been verified and do not receive credence (J. Trop. Med., July 1, 1903).

The most convincing evidence as to mosquito transmission of dengue is that afforded by the absence of dengue in Port Said during the years 1906 and 1907 notwithstanding the prevalence of the disease in adjacent parts of Egypt. This was attributed to the absence of mosquitoes, these having been destroyed in the fight to make Port Said malaria free. This campaign was commenced in May, 1906 (Ross: Ann. Trop. Med. and Parasitol., 1908, 11, 193).

While in the Philippines in 1905-1906 I was struck with the fact that when there were no mosquitoes about the hospital reservation there were no cross infections with dengue among the other and non-immune patients in the same ward. After the onset of the rainy season, however, mosquitoes became abundant and in all probability became infected and subsequently transferred the infection.

At this time I examined many hundreds of the mosquitoes present on our reservation and noted the presence of *Myzomyia ludlowii*, *Stegomyia scutellaris* and but one species of the genus *Culex*, *C. microannulatus*. The determination of the species was made by Prof. Banks, the entomologist of the Bureau of Science. I was not able at that time to find a single specimen of *Culex fatigans*.

In 1909 I returned to the Philippines and a few days after my arrival an officer who had been operated on for appendicitis

[120] suddenly developed a temperature. The blood findings reassured us from a surgical standpoint and by the third day of his fever the case was positively recognized as dengue. At the U. S. Naval Hospital, Canacao, P. I., there are two bungalow-type wards for sick officers. At the time I refer to one ward was perfectly screened, the second less satisfactorily. It was in this building that the case referred to above occurred. Three more similar cases occurring within a few weeks I had this building put out of commission and fumigated with sulphur. During the subsequent two years I remained at Canacao no further cases developed in this building, although dengue cases sent to the hospital from the station and ships were frequently under treatment in it.

[121] In the hospital proper there are four large wards, each ward thoroughly screened and in the two medical wards there are small wire-screened rooms or cages in which any case suspected of being malaria or dengue is immediately placed upon admission to the hospital. It is improbable that a mosquito can gain access to the main ward and almost an impossibility for such insects to effect an entrance into the wire screen cage. Each of these compartments could accommodate nine beds. During the two years I followed this experiment, although more than 200 dengue patients were under treatment in these cages, there were no instances of infection of those lying in the open ward and only separated from the dengue patients by the wire screen.



